JACC Vol. 22, No. 1
July 1993:65–72

CLINICAL STUDIES

HEART FAILURE

Double-Blind, Placebo-Controlled Study of the Efficacy of Flosequinan in Patients With Chronic Heart Failure

MILTON PACKER, MD, FACC,*† KENNETH A. NARAHARA, MD, FACC,‡
URI ELKAYAM, MD, FACC,§ JAY M. SULLIVAN, MD, FACC,‖
DAVID L. PEARLE, MD, FACC,¶ BARRY M. MASSIE, MD, FACC,#
MARK A. CREAGER, MD, FACC** AND THE PRINCIPAL INVESTIGATORS OF THE REFLECT STUDY

New York, New York; Torrance, Los Angeles and San Francisco, California; Memphis, Tennessee; Washington, D.C.; Boston, Massachusetts

Objectives. **The aim of this study was to assess the efficacy of flosequinan in chronic heart failure.**

Background. **Flosequinan is a new vasodilator drug that acts by interfering with the inositol-triphosphate/protein kinase C pathway, an important mechanism of vasoconstriction. The drug dilates both peripheral arteries and veins, is orally active and has a long duration of action that permits once-daily dosing. Previous studies have shown that flosequinan produces sustained hemodynamic benefits in heart failure, but large scale studies evaluating its clinical efficacy have not been reported.**

Methods. **One hundred ninety-three patients with chronic heart failure (New York Heart Association functional class II or III and left ventricular ejection fraction <40%) receiving digoxin and diuretic drugs were randomly assigned (double-blind) to the addition of flosequinan (100 mg once daily, n = 93) or placebo (n = 100) for 3 months. The clinical status and exercise tolerance of each patient was evaluated at the start of the study and every 2 to 4 weeks during the trial while background therapy remained constant.**

Results. **After 12 weeks, maximal treadmill exercise time increased by 96 s in the flosequinan group but by only 47 s in the placebo group ($p = 0.022$ for the difference between groups). Maximal oxygen consumption increased by 1.7 ml/kg per min in the flosequinan group (n = 17) but by only 0.6 ml/kg per min in the placebo group (n = 23), $p = 0.05$ between the groups. Symptomatically, 55% of patients receiving flosequinan but only 36% of patients receiving placebo benefited from treatment ($p = 0.018$). In addition, fewer patients treated with flosequinan had sufficiently severe worsening of heart failure to require a change in medication or withdrawal from the study ($p = 0.07$). By intention to treat, seven patients in the flosequinan group and two patients in the placebo group died.**

Conclusions. **These findings indicate that flosequinan is an effective drug for patients with chronic heart failure who remain symptomatic despite treatment with digoxin and diuretic drugs. The effect of the drug on survival remains to be determined.**

(J Am Coll Cardiol 1993;22:65–72)

Because peripheral vasoconstriction impairs cardiac performance in chronic heart failure (1), vasodilator therapy has emerged as an established approach to the treatment of this disorder. The administration of drugs that dilate peripheral arteries and veins produces hemodynamic and symptomatic improvement in patients with heart failure; moreover, long-term treatment with vasodilators has been shown to reduce the mortality of this disease (2,3). However, currently available vasodilator drugs have important limitations. Some vasodilators fail to produce long-term hemodynamic benefits because tolerance develops to their initial hemodynamic effects (4–6). Others activate neurohormonal mechanisms and cause fluid retention that may limit their symptomatic and prognostic benefits (3,7). Still others depress myocardial contractility and may thereby worsen the clinical condition of patients (8). Finally, most vasodilator drugs produce adverse effects that restrict the usefulness of long-term therapy (2).

Flosequinan is a new vasodilator drug that acts by interfering with the inositol-triphosphate/protein kinase C pathway, an important mechanism of vasoconstriction (9). The drug is orally active and has a long duration of action that permits once-daily dosing (10). By dilating both peripheral arteries and veins (11), flosequinan produces short- (12) and long-term hemodynamic benefits in heart failure (12,13);

*From the Mount Sinai School of Medicine, New York, New York; ‡Los Angeles County Harbor-UCLA Medical Center, Torrance, California; §University of Southern California, Los Angeles, California; ‖University of Tennessee, Memphis, Tennessee; ¶Georgetown University, Washington, D.C.; #Veterans Administration Hospital, University of California, San Francisco, California, and **Brigham and Women's Hospital, Boston, Massachusetts. This study was supported in part by a grant from Boots Pharmaceuticals, Inc., Shreveport, Louisiana and Lincolnshire, Illinois.

Manuscript received September 18, 1992; revised manuscript received January 14, 1993, accepted January 20, 1993.

†Present address and address for correspondence: Milton Packer, MD, Division of Circulatory Physiology and Center for Heart Failure Research, Columbia University, College of Physicians and Surgeons, 630 West 168 Street, New York, New York 10032.

0735-1097/93/$6.00

JACC Vol. 22, No. 1
July 1993:65–72

tolerance has not been reported during prolonged therapy. Furthermore, flosequinan has been well tolerated in early clinical studies. The drug does not cause fluid retention or depress cardiac contractility (14); thus, its use has not been associated with worsening heart failure. Flosequinan has produced clinical benefits in two small controlled trials (15,16), but its effect on symptoms and exercise tolerance has not been evaluated in large scale studies.

We therefore carried out the Randomized Evaluation of FLosequinan on ExerCise Tolerance (REFLECT) study. The primary objective of this trial was to assess the effect of flosequinan on symptoms and exercise capacity in a large group of patients with chronic heart failure who remained symptomatic despite treatment with digitalis and diuretic drugs.

Methods

Patients with chronic heart failure were enrolled at 23 centers in the United States and Canada. Heart failure was defined by the presence of dyspnea or fatigue on exertion in association with a left ventricular ejection fraction ≤40% and a cardiothoracic ratio ≥50%. All patients had subjective and objective evidence for reduced effort tolerance, as demonstrated by New York Heart Association functional class II or III symptoms and an exercise duration (modified Naughton protocol) between 3 and 14 min despite treatment with digitalis and diuretic drugs for ≥2 months. The use of other vasodilators (long-acting nitrates, hydralazine, prazosin, converting-enzyme inhibitors or calcium channel blocking agents) was not permitted, but treatment with antiarrhythmic drugs other than beta-adrenergic blocking agents was allowed. Patients could not participate if they had a primary valvular or pericardial disorder or obstructive or hypertrophic cardiomyopathy. Patients were also excluded if they had any of the following: age <18 years; systolic blood pressure <90 mm Hg; exercise limited by angina, lung disease or claudication; angina requiring continuous treatment; a myocardial infarction within 3 months, or severe primary pulmonary, renal or hepatic disease. The protocol was approved by the Institutional Review Board of all participating institutions.

At the start of the study, patients were queried about their symptoms; vital signs were measured; cardiac size and function were determined (by chest radiography and radionuclide ventriculography, respectively); cardiac arrhythmias were quantified (by a 24-h ambulatory recording), and blood was collected for the evaluation of serum electrolytes, renal function and circulating neurohormonal factors. In addition, patients underwent repeated maximal treadmill exercise testing (using a modified Naughton protocol) until exercise times limited by either dyspnea or fatigue were highly reproducible; specifically, the durations of three consecutive tests were required to be within 60 s of each other and show no trend. This criterion for reproducibility has been shown to minimize the placebo effect that is commonly observed in controlled trials in heart failure (Pinsky DJ et al., unpublished observations). At selected centers, exercise tolerance was also assessed by the evaluation of oxygen consumption using breath-by-breath measurements of expired gases.

After completion of these initial assessments, patients were randomly assigned in double-blind fashion to receive either flosequinan (100 mg orally once daily) or matching placebo, in addition to digoxin and a diuretic drug for 3 months. This dose of flosequinan has been shown to produce long-term hemodynamic benefits with minimal subjective side effects (13). If 100 mg once daily was not tolerated, the dose could be decreased in double-blind manner to 75 mg once daily. During the following 3 months, symptoms and exercise tolerance were evaluated every 2 and 4 weeks, respectively. Every effort was made to keep doses of concomitantly administered cardioactive drugs constant, but the doses of diuretic drugs could be adjusted if body weight increased >2 kg. Patients were not permitted to receive open label flosequinan. At the end of the study, all assessments carried out at the start of the study were repeated.

Statistical analysis. The primary objective of the study, as specified in the original protocol, was to compare the change in exercise tolerance in the placebo and flosequinan treatment groups after 12 weeks of therapy. The sample size was estimated to be 150 patients based on the assumption that the difference in the exercise response between the two groups would be 60 s with an SD of 75 s (power = 0.80, alpha = 0.05).

The baseline characteristics of the two treatment groups were compared by the *t* test (for continuous variables) and the Fisher exact test (for categorical variables). Treatment effects were assessed by comparing the change in one group with the change in the other. Analyses were carried out on all available data (using carry forward methods) according to the patients' original randomized assignment (intention to treat principle). Comparisons were performed by analysis of variance (Tables 2 and 3) or Fisher exact test (Table 4, Fig. 3). Appropriate nonparametric methods (the median test [17]) were used when the data displayed marked nonnormality (Fig. 1). General linear models for categorical data were used for the analyses in Figure 2.

Results

Patient groups. One hundred ninety-three patients (168 men, 25 women) were enrolled in the REFLECT study. The cause of heart failure was ischemic heart disease in 84 patients and idiopathic cardiomyopathy in 109; 81 patients had class II and 112 patients had class III symptoms. The mean left ventricular ejection fraction was 0.26. All but five patients were receiving digoxin, and the mean dose of furosemide prescribed was 88 mg daily. Within 4 weeks of enrollment, 27% of patients had received a converting enzyme inhibitor, which was discontinued at least 2 weeks before entry into the study.

Table 1. Baseline Characteristics of Patients Before Randomization*

	Placebo (n = 100)	Flosequinan (n = 93)
Demographic characteristics		
Age (yr)	57.2 ± 1.3	58.2 ± 1.1
Male/female	87/13	81/12
Weight (kg)	82.2 ± 2.1	82.1 ± 2.1
Cause of heart failure		
Ischemic heart disease	46	38
Primary cardiomyopathy	54	55
Concomitant medications		
Digoxin use (%)	96	96
Daily dose of furosemide (mg/day)	90 ± 7	88 ± 7
Prior treatment with nitrates (%)	34	25
Prior treatment with hydralazine (%)	4	6
Prior treatment with ACE inhibitors (%)	28	26
Hemodynamic measurements		
Cardiothoracic ratio	0.60 ± 0.01	0.60 ± 0.01
LV ejection fraction	0.26 ± 0.01	0.25 ± 0.01
Supine systolic blood pressure (mm Hg)	123 ± 3	125 ± 2
Supine diastolic blood pressure (mm Hg)	76 ± 1	79 ± 1
Heart rate (beats/min)	82 ± 2	80 ± 1
Functional measurements		
NYHA functional class (II/III)	42/58	39/54
Exercise duration (s)	520 ± 17	536 ± 18
Maximal oxygen consumption (ml/kg per min)	14.2 ± 0.9	11.5 ± 0.9
Biochemical measurements		
Serum sodium concentration (mEq/liter)	139 ± 0.3	140 ± 0.4
Serum potassium concentration (mEq/liter)	4.2 ± 0.1	4.2 ± 0.1
Blood urea nitrogen (mg/dl)	20 ± 1	21 ± 1
Serum creatinine concentration (mg/dl)	1.4 ± 0.03	1.4 ± 0.04
Neurohormonal measurements		
Plasma norepinephrine (pg/ml)	338 ± 42	378 ± 43
Plasma renin activity (ng/ml per h)	4.3 ± 1.8	4.7 ± 0.9
Plasma arginine vasopressin (pg/ml)	3.4 ± 0.5	2.8 ± 0.3
Plasma atrial natriuretic peptide (pg/ml)	140 ± 19	114 ± 12
Electrocardiographic measurements		
Patients with >30 VPB/h (%)	62	54
Patients with ventricular tachycardia (%)	71	74

*No differences between groups were statistically significant. Data are expressed as number or percent of patients or mean value ± SEM. Neurohormonal, ambulatory, electrocardiographic and oxygen consumption measurements were obtained in 55, 81 and 47 patients, respectively. ACE = angiotensin-converting enzyme; LV = left ventricular; NYHA = New York Heart Association; VPB = ventricular premature beats.

Of the 193 patients, 93 were randomly assigned to flosequinan and 100 were assigned to placebo. The two groups were similar with respect to all pretreatment variables (Table 1), including age, gender, cause and severity of heart failure, noninvasive measures of cardiac function, exercise duration, vital signs, use of digoxin and diuretic drugs and prior use of converting enzyme inhibitors and direct acting vasodilators. All but four patients received 100 mg of flosequinan once daily or placebo; four patients (all randomized to flosequinan therapy) received 75 mg once daily because they experienced dizziness or tachycardia, or both, while receiving 100 mg. Of the 193 randomized patients, 8 patients (2 receiving placebo, 6 receiving flosequinan) were withdrawn from the study before the first double-blind symptom assessment at 2 weeks; and 21 patients (9 receiving placebo, 12 receiving flosequinan) were withdrawn before the first double-blind exercise tolerance test at 4 weeks. Thus, whereas safety was evaluated in all 193 patients, symptoms were assessed in 185 patients (98 receiving placebo, 87 receiving flosequinan) and exercise tolerance in 172 patients (91 receiving placebo, 81 receiving flosequinan).

Effect on exercise tolerance. During double-blind therapy, exercise capacity improved more in patients randomized to flosequinan than in those randomized to placebo (Fig. 1). After 12 weeks, exercise tolerance increased by 96 s in the flosequinan group but by only 47 s in the placebo group ($p = 0.022$ comparing the two groups). Figure 2 shows the proportion of patients in each group who had a favorable exercise response, defined as an increase in exercise duration of ≥60 s, ≥90 s or ≥120 s over pretreatment values.

JACC Vol. 22, No. 1
July 1993:65–72

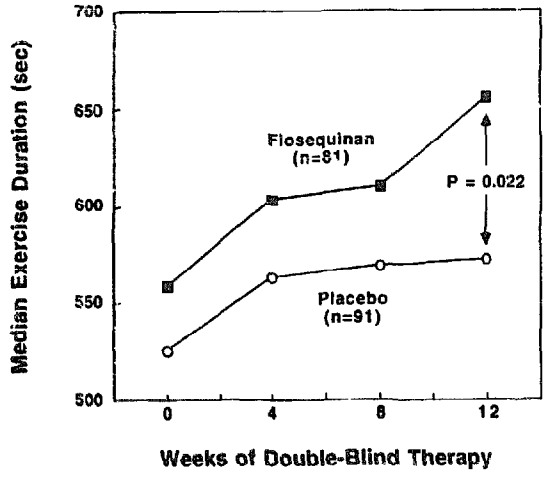


Figure 1. Median duration of treadmill exercise (modified Naughton protocol) in the flosequinan and placebo groups at the time of randomization (0 weeks) and after 4, 8 and 12 weeks of double-blind therapy. After 12 weeks the median change in exercise duration in the flosequinan group (**closed squares**) was significantly greater than the median change in exercise duration in the placebo group (**open circles**) (+96 vs. +47 s; p = 0.022).

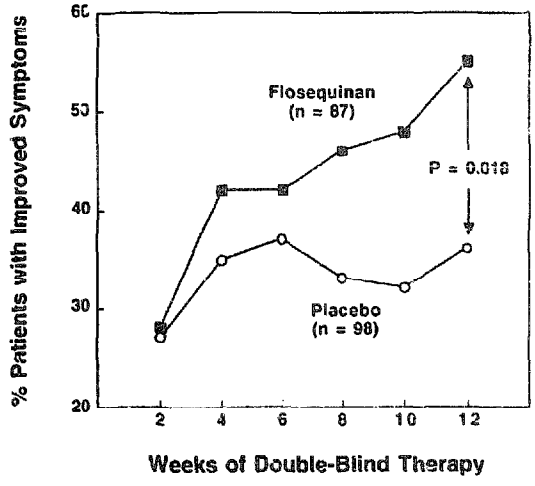
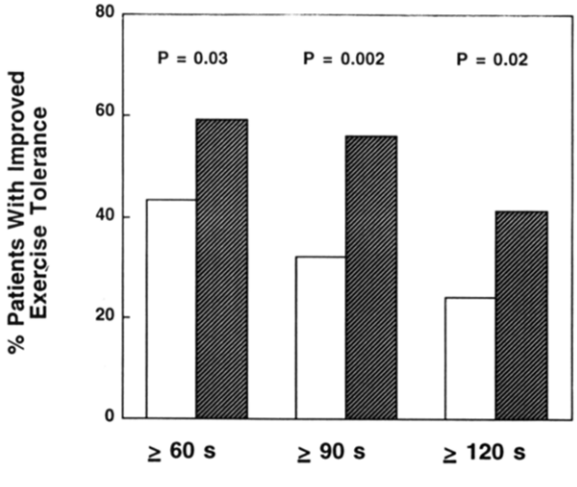


Figure 3. Proportion of patients who reported lessening of symptoms of heart failure and enhanced overall sense of well-being in the flosequinan group (**closed squares**) and in the placebo group (**open circles**) after 2, 4, 6, 8, 10 and 12 weeks of double-blind therapy. After 12 weeks, 55% of patients in the flosequinan group but only 36% of the patients in the placebo group had clinical improvement, p = 0.018. The time course of improvement in symptoms closely paralleled the time course of improvement in exercise tolerance (compare Fig. 1 and Fig. 3).

Regardless of which criteria are used, there are more responders in the flosequinan group than in the placebo group ($p < 0.05$ for all three criteria). When exercise capacity was assessed by the measurement of respiratory gas exchange, maximal oxygen consumption increased by 1.7 ml/kg per min in the flosequinan group (n = 17) but by only 0.6 ml/kg per min in the placebo group (n = 23), p = 0.05 comparing the two groups.

The effect of flosequinan on exercise capacity was not dependent on the patient's pretreatment functional class or left ventricular ejection fraction. The placebo-corrected increase in exercise time produced by flosequinan was similar in patients with class II or class III symptoms (+58 and +46 s, respectively) and in patients with an ejection fraction ≤0.20 or >0.30 (+42 and +49 s, respectively).

Figure 2. Proportion of patients in the placebo group (**clear bars**) and in the flosequinan group (**shaded bars**) who had a favorable exercise response, defined by three different criteria: 1) an increase in exercise duration ≥60 s over baseline; 2) an increase in exercise duration ≥90 s over baseline; and 3) an increase in exercise duration ≥120 s over baseline. Regardless of which criterion was used, the proportion of responders was greater in the flosequinan group than in the placebo group (all $p < 0.05$).



Effect on symptoms of heart failure. During the 1st 2 weeks of double-blind therapy, a similar proportion (25% to 30%) of patients in the two treatment groups improved clinically. However, after 4 to 12 weeks of therapy, more patients in the flosequinan than in the placebo group were considered by the investigator to have symptomatic improvement and to show an enhanced overall sense of well-being (Fig. 3). The pattern of improvement in the clinical status of patients paralleled the pattern of improvement in their exercise tolerance (compare Fig. 1 and 3). At the end of the study, 55% of patients receiving flosequinan but only 36% of patients receiving placebo benefited from treatment (p = 0.018). In addition, 19% of patients receiving placebo but only 10% of patients receiving flosequinan had worsening heart failure that was sufficiently severe to require an increased dose of diuretic drugs or withdrawal from the study (p = 0.07). Flosequinan produced no change in functional class, cardiothoracic ratio or left ventricular ejection fraction (Table 2).

Effect on safety. Compared with the changes seen in the placebo group, long-term therapy with flosequinan was associated with a significant decrease in supine systolic blood pressure (−7 mm Hg) and increase in supine and standing heart rate (+8 and +7 beats/min, respectively), both $p < 0.05$, without a change in standing systolic blood

Table 2. Effect of Flosequinan on Hemodynamic Measurements in Patients With Chronic Heart Failure

	Placebo		Flosequinan		
	Baseline	Treatment	Baseline	Treatment	p Value
Supine systolic blood pressure (mm Hg)	122 ± 2	125 ± 2	124 ± 2	120 ± 2	0.02
Supine diastolic blood pressure (mm Hg)	78 ± 1	79 ± 1	79 ± 1	77 ± 1	NS
Supine heart rate (beats/min)	84 ± 2	82 ± 2	82 ± 2	88 ± 2	< 0.001
Standing systolic blood pressure (mm Hg)	122 ± 2	124 ± 2	123 ± 2	119 ± 2	NS
Standing diastolic blood pressure (mm Hg)	79 ± 1	79 ± 1	78 ± 1	77 ± 1	NS
Standing heart rate (beats/min)	88 ± 1	86 ± 1	87 ± 2	92 ± 2	< 0.001
Body weight (kg)	82 ± 2	83 ± 2	82 ± 2	82 ± 2	NS
Cardiothoracic ratio	0.59 ± 0.01	0.57 ± 0.01	0.60 ± 0.01	0.57 ± 0.01	NS
LV ejection fraction	0.28 ± 0.02	0.30 ± 0.02	0.25 ± 0.02	0.24 ± 0.02	NS

All values are expressed as mean value ± SEM. Data are shown only for patients with both pretreatment and posttreatment values. Paired data for cardiothoracic ratio and left ventricular (LV) ejection fraction were collected in 147 and 30 patients, respectively. p value denotes significance of between-group differences.

pressure or supine or standing diastolic blood pressure (Table 2). The drug produced no significant changes in body weight or orthostatic changes in blood pressure.

Flosequinan produced no important changes in laboratory tests (Table 3) except that serum bilirubin decreased slightly (by 0.2 mg/dl, p = 0.03) in patients treated with the drug. Therapy with flosequinan was associated with an increase in plasma norepinephrine (p = 0.08) without notable changes in plasma renin activity, arginine vasopressin or atrial natriuretic peptide (Table 3). The drug was not associated with any proarrhythmic effects. As assessed by criteria modified from those proposed by Morganroth et al. (18), proarrhythmia was observed in six patients receiving placebo and four patients receiving flosequinan.

The frequency of reported side effects in the study was similar in the two treatment groups (Table 4). Adverse reactions attributable to peripheral vasodilation (headache, dizziness, palpitation and tachycardia) were more common in flosequinan-treated patients, but only the frequency of headaches was significantly different (22% with flosequinan vs. 9% with placebo, p = 0.04). These vasodilator-type side effects were generally mild and short-lived and rarely required discontinuation of therapy (Table 5). Overall, 30% of patients treated with flosequinan and 33% of patients treated with placebo were withdrawn from double-blind therapy. The most common reason for withdrawal was worsening heart failure, which occurred more frequently in the placebo group.

During double-blind therapy, eight patients died (six in the flosequinan group and two in the placebo group). The mode of death was sudden in seven patients (five in the flosequinan and two in the placebo group), and one patient in the flosequinan group died after an acute myocardial infarction. One additional patient randomized to flosequinan died suddenly within 12 weeks of randomization, but this death occurred 16 days after withdrawal from the study for administrative reasons; the patient required treatment with an antiarrhythmic drug that was prohibited by the protocol. Hence, when analyzed by intention to treat, there were seven deaths in the flosequinan group and two in the placebo group (p > 0.10).

Table 3. Effect of Flosequinan on Biochemical and Neurohormonal Measurements in Patients With Chronic Heart Failure

	Placebo		Flosequinan		
	Baseline	Treatment	Baseline	Treatment	p Value
Serum sodium concentration (mmol/liter)	139 ± 0.3	139 ± 0.4	140 ± 0.4	139 ± 0.4	NS
Serum potassium concentration (mmol/liter)	4.2 ± 0.1	4.1 ± 0.1	4.2 ± 0.1	3.9 ± 0.1	NS
Blood urea nitrogen (mg/dl)	20 ± 1	20 ± 1	21 ± 1	20 ± 1	NS
Serum creatinine concentration (mg/dl)	1.4 ± 0.03	1.4 ± 0.04	1.4 ± 0.04	1.5 ± 0.04	NS
Serum cholesterol (mg/dl)	214 ± 5	213 ± 5	207 ± 5	208 ± 5	NS
Total bilirubin (mg/dl)	0.7 ± 0.04	0.7 ± 0.04	0.8 ± 0.05	0.7 ± 0.06	0.03
Alkaline phosphatase (mU/ml)	91 ± 4	88 ± 4	92 ± 5	90 ± 4	NS
Serum aspartate aminotransferase (mU/ml)	24 ± 1	24 ± 1	22 ± 1	22 ± 1	NS
Serum alanine aminotransferase (mU/ml)	25 ± 2	23 ± 1	20 ± 1	19 ± 1	NS
Hemoglobin (ml/dl)	14.1 ± 0.2	14.3 ± 0.2	14.3 ± 0.2	14.0 ± 0.2	NS
White blood count (× 10^3/ml)	7.2 ± 0.2	7.3 ± 0.2	7.2 ± 0.2	6.9 ± 0.2	NS
Plasma norepinephrine (pg/ml)	337 ± 43	319 ± 39	400 ± 46	476 ± 51	0.08
Plasma renin activity (mg/ml per h)	4.6 ± 1.9	4.8 ± 2.1	4.6 ± 1.0	5.4 ± 1.2	NS
Plasma arginine vasopressin (pg/ml)	3.5 ± 0.5	2.8 ± 0.4	2.7 ± 0.3	2.8 ± 0.3	NS
Plasma atrial natriuretic peptide (pg/ml)	133 ± 18	125 ± 18	112 ± 13	88 ± 11	NS

p value denotes significance of between-group differences.

JACC Vol. 22, No. 1
July 1993:65–72

Table 4. Adverse Events During the Study

	Placebo (n = 100)	Flosequinan (n = 93)	p Value
At least one adverse effect (%)	68	71	NS
Cardiopulmonary symptoms (%)			
Angina	0 (0)	1 (1)	NS
Dizziness/vertigo	5 (5)	10 (11)	NS
Edema	7 (7)	2 (2)	NS
Hypotension	0 (0)	2 (2)	NS
Palpitation	3 (3)	7 (7)	NS
Myocardial infarction	2 (2)	3 (3)	NS
Syncope	0 (0)	1 (1)	NS
Tachycardia	0 (0)	4 (4)	NS
Noncardiopulmonary symptoms (%)			
Anorexia	1 (1)	3 (3)	NS
Cough	4 (4)	2 (2)	NS
Diarrhea	4 (4)	3 (3)	NS
Headache	9 (9)	20 (22)	0.04
Nausea	1 (1)	6 (6)	NS
Rash/pruritus	4 (4)	0 (0)	NS
Taste disturbance	0 (0)	2 (2)	NS

Data are expressed as number (%) of patients.

Discussion

The results of this multicenter, placebo-controlled study indicate that flosequinan produces clinical benefits when administered to patients with chronic heart failure who remain symptomatic despite treatment with digitalis and diuretic drugs. Flosequinan enhanced the symptomatic status and well-being of patients in our study and reduced the risk of worsening heart failure. The drug improved exercise capacity as assessed by either the duration of treadmill exercise or the measurement of maximal oxygen consumption. Finally, flosequinan was subjectively well tolerated by the patients in our study. Although some patients experienced side effects attributable to the drug's vasodilator actions, these were mild and short-lived and generally did not require discontinuation of therapy. The incidence of laboratory abnormalities was similar in the flosequinan and placebo treatment groups, and therapy with the drug was not associated with many of the side effects (for example, proarrhythmia or fluid retention) that have limited the utility of other drugs for heart failure. The findings of this large scale study confirm the results of smaller trials (15,16) that have shown that flosequinan is an effective treatment for chronic heart failure.

Table 5. Reasons for Withdrawal From the Study During Double-Blind Therapy

	Placebo (n = 100)	Flosequinan (n = 93)
Cardiopulmonary events		
Worsening heart failure	10	6
Acute myocardial infarction	1	2 (1*)
Chest pain syndrome	0	1
Ventricular arrhythmia	0	1
Bradycardia	1	0
Sudden death	2 (2*)	5 (5*)
First dose hypotension	0	1
Cardiac transplantation	1	0
Flulike syndrome	1	0
Noncardiopulmonary events		
Protocol violation	6	4
Noncompliance	2	2
Patient request	3	0
Administrative reasons	3	3 (1*†)
Headache	1	1
Leg problems	1	2
Hemolytic anemia	1	0
Total	33	28

*Number of patients who died by intention to treat analysis. Eight of the nine deaths (seven sudden and one after an acute myocardial infarction) occurred during double-blind therapy. †One patient died suddenly 16 days after withdrawal from the study for administrative reasons; the patient required treatment with an antiarrhythmic drug that was prohibited by the protocol.

Comparison of flosequinan with other drugs for heart failure. The benefits of flosequinan in this study are similar to those previously reported in controlled exercise trials of converting enzyme inhibitors in chronic heart failure (19–21). Both flosequinan and the converting enzyme inhibitors are effective in patients in functional class II or III who remain symptomatic despite therapy with digoxin and diuretic drugs. Both flosequinan and the converting enzyme inhibitors alleviate the symptoms of heart failure, and this benefit is paralleled by a similar increase in exercise capacity (approximately 50 to 60 s using a modified Naughton protocol) (19–21). With both classes of drugs, the improvement in exercise tolerance is not seen immediately after the institution of therapy but becomes apparent only after patients are treated for several months (Fig. 1); the pathophysiologic mechanisms underlying this delay are not understood (19,21). Because of these similarities, flosequinan may be useful in patients who cannot tolerate or should not receive converting enzyme inhibitors, because use of the drug is not associated with many of the side effects of the converting enzyme inhibitors (such as first-dose hypotension, cough, rash or renal insufficiency).

The responses to flosequinan also resemble the responses seen with the combination of hydralazine and isosorbide dinitrate in patients with chronic heart failure. Both flosequinan and the combination of hydralazine and isosorbide dinitrate produce similar hemodynamic effects (12,13,22,23). This response is primarily the result of a direct dilating effect of these drugs on peripheral arteries and veins, although both flosequinan and hydralazine also exert direct positive inotropic and chronotropic effects (14,24,25). Both flosequinan and the vasodilator combination have been shown to improve the symptoms and exercise tolerance of patients with heart failure in controlled clinical trials (3,15,16). However, the administration of flosequinan is more convenient and may be subjectively better tolerated than the combination of isosorbide dinitrate and hydralazine. Whereas the vasodilator combination requires multiple dosing each day

and produces side effects that commonly limit therapy (2), flosequinan is given in a single daily dose and the frequency of side effects requiring the discontinuation of treatment is similar to that seen in patients treated with placebo. Furthermore, whereas the hemodynamic benefits of both isosorbide dinitrate and hydralazine may become attenuated during long-term therapy (26,27), pharmacologic tolerance has not been reported with flosequinan.

The effects of flosequinan in our study differ from those reported (8,28) with some vasodilator drugs—specifically, minoxidil and calcium channel blockers—which may cause worsening heart failure during long-term use. This risk of clinical deterioration has been attributed to the predilection of these drugs to depress cardiac contractility and cause sodium retention. However, unlike minoxidil and nifedipine, flosequinan reduced the risk of worsening heart failure in our study, possibly because the drug does not depress contractility (14) or cause edema or fluid retention.

Mechanisms of action of flosequinan. The differences between flosequinan and other vasodilator drugs outlined in the previous paragraphs may be related to flosequinan's unique mechanism of action. Flosequinan does not interact with adrenergic, purinergic or serotonergic receptors or with calmodulin; it does not affect calcium or potassium channels; it does not inhibit actomyosin adenosine triphosphatase or the angiotensin-converting enzyme; and its action does not depend on the release of endothelium-derived relaxing factor or on the synthesis of prostaglandins or thromboxane. The observation that flosequinan antagonizes the constriction produced by a variety of endogenous vasoconstrictors (norepinephrine, angiotensin II and endothelin) (Yates D, personal communication, 1992) has led investigators to postulate that the drug interferes with a principal common pathway regulating the handling of intracellular calcium in vascular smooth muscle. The specific site of action of flosequinan appears to be the inositol-triphosphate/protein kinase C pathway, because the drug attenuates the increase in both of these intracellular second messengers that follows exposure to endogenous vasoconstrictors (endothelin, for example) (9). Such a mechanism of action may be unique among clinically available vasodilators.

Effect of flosequinan on survival. The effect of flosequinan on the survival of patients with chronic heart failure is not known. To the extent that the drug exerts actions similar to that of converting enzyme inhibitors or a combination of hydralazine and isosorbide dinitrate, we might expect therapy with flosequinan to prolong life in patients with chronic heart failure (2). However, in the doses used in the present trial, flosequinan increased heart rate and plasma norepinephrine and can increase myocardial contractility (14). These effects appear to be direct actions of the drug because they cannot be explained by a reflex response to flosequinan's vasodilator properties (29), and these actions are characteristic of drugs that have an adverse effect on mortality (30,31). Concerns that flosequinan might adversely affect mortality are heightened by the finding in the present study that seven patients died in the flosequinan group whereas two died in the placebo group. The small number of events makes it difficult to interpret these data, but the possibility that flosequinan (like milrinone [31]) may increase mortality cannot be ruled out. Yet, unlike milrinone (32), flosequinan does not increase myocardial cyclic adenosine monophosphate (33,34), and its use was not associated with proarrhythmic effects in the present study. Nevertheless, the effect of flosequinan on the survival of patients with chronic heart failure remains an important issue that is now being evaluated in an ongoing study of 3,500 patients (Prospective Randomized Flosequinan Longevity Evaluation [PROFILE]).

Conclusions. The present study demonstrates that flosequinan (75 to 100 mg once daily) is an effective and well tolerated drug for the management of patients with heart failure who remain symptomatic despite treatment with digoxin and diuretic drugs. The results of this study were recently confirmed by two other large scale trials (REFLECT II and FACET [35,36]); in the latter study, flosequinan was effective in patients who remained symptomatic despite the use of converting enzyme inhibitors. The effect of the drug on survival requires further study.

Appendix

Study Organization

Steering Committee

Milton Packer, MD (chair), Mark A. Creager, MD, Uri Elkayam, MD, Barry M. Massie, MD, Kenneth A. Narahara, MD, David L. Pearle, MD, Jay M. Sullivan, MD

Participating Centers and Principal Investigators

Boston, MA (Harvard Medical School, Brigham and Women's Hospital): Mark A. Creager, MD, Wilson S. Colucci, MD, Shelly J. Gallagher, BSN

Chalmette, LA: Bruce Iteld, MD, Zelma Morris, RN

Detroit, MI (Henry Ford Hospital): T. Barry Levine, MD, Denise Budzinski, RN

Lombard, IL (Midwest Center for Heart Failure): Marc A. Silver, MD, Lorraine Heaney, RN, Carol Keeler, RN

London, Ontario (University of Western Ontario, Victoria Hospital): J. Malcolm Arnold, MD, Gail Burton, RN

Long Beach, CA (VA Medical Center): Victor Froelicher, MD, Susan Forbes, RN

Los Angeles, CA (University of Southern California School of Medicine): Uri Elkayam, MD, Laura Weber, RN

Madison, WI (University of Wisconsin): Condor R. Vander Ark, MD, Peggy Weiderholt, RN

Memphis, TN (University of Tennessee College of Medicine): Jay M. Sullivan, MD, Phyllis Coleman, RN

Miami FL (University of Miami School of Medicine): Donald J. Weidler, MD, PhD, Elizabeth Smith, RN

New Orleans, LA (Tulane University Medical Center): Thomas D. Giles, MD, Louise Roffidal, RN

New York, NY (Mount Sinai School of Medicine, VA Medical Center): Milton Packer, MD, Marrick L. Kukin, MD, Peter B. Wilson, MD, David J. Pinsky, MD, Deborah Ahern, RN

Oklahoma City, OK (University of Oklahoma Health Sciences Center and VA Medical Center): Udho Thadani, MD, Shala Klutts, RN

Philadelphia, PA (University of Pennsylvania School of Medicine, Presbyterian Medical Center): Mariell Jessup, MD, Judianne Samaha, RN

Portland, OR (Oregon Health Sciences University): Barry Greenberg, MD, Maureen Lind, RN

San Antonio, TX (Wilford Hall USAF Medical Center): Leo Spaccavento, MD, Mary Jane Burns, RN

San Diego, CA (University of California, VA Medical Center): Alan S. Maisel, MD, Helen Stamler, RN

San Francisco, CA (Letterman Army Medical Center): William D. Bowden, DO

San Francisco, CA (University of California, VA Medical Center): Barry M. Massie, MD, Ernest Haeusslein, MD, Nina Topaz, RN

Shreveport, LA (VA Medical Center): Michael Owens, MD, Pam Rasache, RRT

Takoma Park, MD (Washington Adventist Hospital): Robert DiBianco, MD, Donna Lindemuth, RN

Torrance, CA (Harbor-UCLA Medical Center): Kenneth A. Narahara, MD, Marianne Brizendine, RN, Hazel Kawasaki, RN, Jean Muller, MD, Leona Lochmiller

Washington, D.C. (Georgetown University Hospital): David L. Pearle, MD, Kathy Matthews, RN

References

1. Cohn JN. Vasodilator therapy for heart failure: the influence of impedance on left ventricular performance. Circulation 1973;48:5–8.
2. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.
3. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
4. Packer M, Gottlieb SS, Kessler PD, Medina N, Yushak M. Prevention and reversal of nitrate tolerance in patients with congestive heart failure. N Engl J Med 1987;317:799–804.
5. Packer M, Meller J, Medina N, Yushak M, Gorlin R. Hemodynamic characterization of tolerance to long-term hydralazine therapy in severe chronic heart failure. N Engl J Med 1982;306:57–62.
6. Packer M, Medina N, Yushak M. Role of the renin-angiotensin system in the development of hemodynamic and clinical tolerance to long-term prazosin therapy in patients with severe chronic heart failure. J Am Coll Cardiol 1986;7:671–80.
7. Barjon J-N, Rouleau J-L, Bichet D, Juneau C, De Champlain J. Chronic renal and neurohumoral effects of the calcium entry blocker nisoldipine in patients with congestive heart failure. J Am Coll Cardiol 1987;9:622–30.
8. Elkayam U, Amin J, Mehra A, Vasquez J, Weber L, Rahimtoola SH. A prospective, randomized, double-blind, crossover study to compare the efficacy and safety of chronic nifedipine therapy to isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990;82:1954–61.
9. Lang D, Lewis MJ. The effects of flosequinan on endothelin-1-induced changes in inositol 1,4,5-triphosphate levels and protein kinase C activity in rat aorta. Eur J Pharmacol 1992;226:259–64.
10. Wynne RD, Crampton EL, Hind ID. The pharmacokinetics and haemodynamics of BTS 49465 and its major metabolite in healthy volunteers. Eur J Clin Pharmacol 1985;28:659–64.
11. Cowley AJ, Wynne RD, Hampton JR. The effects of BTS 49465 on blood pressure and peripheral arteriolar and venous tone in normal volunteers. J Hypertens 1984;2(suppl 3):547–9.
12. Kessler PD, Packer M. Hemodynamic effects of BTS 49465, a new long-acting systemic vasodilator drug, in patients with severe congestive heart failure. Am Heart J 1987;113:137–43.
13. Gottlieb SS, Kukin ML, Medina N, Yushak M, Packer M. Sustained hemodynamic response to flosequinan in patients with chronic heart failure receiving converting-enzyme inhibitors (abstr). Circulation 1991; 84(suppl II):II-241.
14. Corin WJ, Monrad ES, Storm JA, Giustino S, Sonnenblick ES, Lejemtel TH. Flosequinan—a vasodilator with positive inotropic activity. Am Heart J 1991;121:537–40.
15. Cowley AJ, Wynne RD, Stainer K, Fullwood L, Rowley JM, Hampton JR. Flosequinan in heart failure: acute hemodynamic and longer term symptomatic effects. Br Med J 1988;297:169–73.
16. Elborn JS, Stanford CF, Nicholls DP. Effect of flosequinan on exercise capacity and symptoms in severe heart failure. Br Heart J 1989;61:331–5.
17. Steel RGD, Torrie JH. Principles and Procedures of Statistics. New York, McGraw-Hill, 1960:403.
18. Morganroth J, Borland M, Chao G. Application of a frequency definition of ventricular proarrhythmia. Am J Cardiol 1987;59:97–9.
19. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983;2:755–63.
20. The Captopril-Digoxin Multicenter Research Group. Comparative effects of captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539–44.
21. Creager MA, Massie BM, Faxon DP, et al. Acute and long-term effects of enalapril on the cardiovascular response to exercise and exercise tolerance in patients with congestive heart failure. J Am Coll Cardiol 1985;6: 163–70.
22. Massie B, Chatterjee K, Werner W, Greenberg B, Hart R, Parmley WW. Hemodynamic advantage of combined administration of hydralazine orally and nitrates nonparenterally on the vasodilator therapy of chronic heart failure. Am J Cardiol 1977;40:794–801.
23. Pierpont GL, Cohn JN, Franciosa JA. Combined oral hydralazine-nitrate therapy in left ventricular failure: hemodynamic equivalency to sodium nitroprusside. Chest 1978;73:8–13.
24. Leier CV, Desch CE, Magorien RD, et al. Positive inotropic effects of hydralazine in human subjects: comparison with prazosin in the setting of congestive heart failure. Am J Cardiol 1980;46:1039–44.
25. Magorien RD, Unverferth DV, Leier CV. Hydralazine therapy in chronic congestive heart failure: sustained central and regional hemodynamic responses. Am J Med 1984;77:267–74.
26. Packer M, Meller J, Medina N, Yushak M, Gorlin R. Hemodynamic characterization of tolerance to long-term hydralazine therapy in severe chronic heart failure. N Engl J Med 1982;306:57–62.
27. Elkayam U, Roth A, Mehra A, et al. Randomized study to evaluate the relation between oral isosorbide dinitrate dosing interval and the development of early tolerance to its effect on left ventricular filling pressure in patients with chronic heart failure. Circulation 1991;84:2040–8.
28. Franciosa JA, Jordan RA, Wilen MM, Leddy CL. Minoxidil in patients with left heart failure: contrasting hemodynamic and clinical effects in a controlled trial. Circulation 1984;70:63–9.
29. Binkley PF, Nunziata E, Hattor P, Proicsy G, Cody RI. Flosequinan augments parasympathetic tone and attenuates sympathetic drive in congestive heart failure: demonstration by analysis of heart rate variability (abstr). J Am Coll Cardiol 1992;19:147A.
30. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–54.
31. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468–75.
32. Kukin ML, Massie BM, Hendrix GH, et al. Characterization of the proarrhythmic effects of oral milrinone in severe heart failure: The PROMISE Study (abstr). J Am Coll Cardiol 1992;19:260A.
33. Perreault CL, Hague NL, Hunneyball IM, Sim MF, Morgan JP. Lack of inotropic response to flosequinan in ventricular muscle from patients with end-stage heart failure (abstr). Circulation 1991;84(suppl II):II-242.
34. Miao L, Hurrell DG, Perreault CL, Morgan JP. Cyclic AMP-independent inotropic action of flosequinan (abstr). Circulation 1992;86(suppl I):I-622.
35. Pitt B and the Reflect II Study Group. A randomized, multicenter, double-blind placebo-controlled study of the efficacy of flosequinan on patients with chronic heart failure (abstr). Circulation 1991;84(suppl II):II-311.
36. Massie BM, Berk MR, Brozena S, et al. Can further benefit be achieved by adding a vasodilator to triple therapy in heart failure: results of the Flosequinan-ACE Inhibitor Trial (FACET) (abstr)? Circulation 1992; 86(suppl I):I-645.